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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/802,686	03/09/2001	Gary Van Nest	377882000900	9981

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MORRISON & FOERSTER LLP
755 PAGE MILL RD
PALO ALTO, CA 94304-1018

EXAMINER	
BROWN, TIMOTHY M	

ART UNIT	PAPER NUMBER
1648	

DATE MAILED: 10/18/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/802,686	VAN NEST, GARY	
	Examiner	Art Unit	
	Timothy M. Brown	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 August 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-6 and 8-15* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6 and 8-15* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

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DETAILED ACTION

This Non-Final Office Action is responsive to the communication received August 2, 2005. Claims 1-6 and 8-15 are under examination.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-6 and 8-15 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention without undue experimentation.

The existence of undue experimentation is determined by the following factors: the breadth of the claims; the nature of the invention; the state of the prior art; the level of one of ordinary skill; the level of predictability in the art; the amount of direction provided by the inventor; the existence of working examples; and the quantity of experimentation needed to make or use the invention based on the content of the disclosure. *In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404.

Applicant claims a method of suppressing RSV infection in an individual who has been exposed to RSV comprising administering a immunostimulatory sequence (ISS) comprising the

sequence 5' - CG –3', wherein the ISS is not administered in conjunction with RSV antigen, immunostimulatory cytokines or any other adjuvant.

The breadth of the claims allows them to read on treating RSV infection in any mammal by administering an ISS without coadministering an RSV antigen.

Regarding the administration of ISS without RSV antigen, the state of the art at the time this application was filed provided that an ISS could be administered as an adjuvant to increase vaccine efficacy. It was known that ISS were capable of increasing Th1 activity by enhancing the production of immunostimulatory cytokines by antigen presenting cells. However, the ability of increased Th1 activity to impact infection still depended on the presence (i.e. administration of) a disease specific antigen (Kobayashi, H. (1999) Cell. Imun. 198, 69-75). This is not surprising since the activity of Th1 cells is modulated by antigen/ MHC complexes on the surface of target macrophage cells. Thus, without the co-administration of an antigen, one skilled in the art could not predict how an ISS, administered alone, could impact infection by a specific pathogen. The directions in the specification do not teach one skilled in the art how this could be accomplished. The specification only teaches administering RSV antigen after pre-priming with ISS (see e.g. Example 2). There is no teaching or working example of suppressing infection by administering ISS alone. This is consistent with the state of the art at the time of filing which only showed the administration of ISS as a pre-priming adjuvant (Kobayashi, H. (1999) Cell. Imun. 198, 69-75). Thus, one skilled in the art would have to determine how to avoid the requirement of antigen in inducing a specific immune response. This experimentation would be extensive and undue since this application was filed at a time when the paradigm held that an immune response against a specific pathogen at least required the recognition of antigen.

Turning to the stimulation of an immune response in any mammal, the specification does not enable using the range of ISS claimed across multiple species. The state of the art the time the application was filed showed that the effects of an ISS were across species could not be predicted. Advances after Applicant's filing date confirm this. Structure-activity studies show that an ISS that has an immunostimulatory effect in mice may not produce the same effect in humans (Fearon, K. (2003) Eur. J. Immunol. 33, 2114-212). Modern research also shows that the ability of ISS to work across species largely depends on the sequences that flank the ISS' CpG dinucleotides. Marshall et al.[1] showed that the ability of an ISS to stimulate an immune response in both mice and humans depends on the presence of specific flanking sequences. In particular, Marshall et al. show that CpG-C sequences, which are flanked by a TCG element near the 5' end of the ISS, are required for stimulation across multiple species. The direction of the specification however fails to teach one skilled in the art how to use the claimed ISS that lack this element to stimulate an immune response across different mammals. Indeed, given the complexity of the immune response and the failure to indicate any other structural elements that work across species, one skilled in the art would have to invest undue experimentation to make and use the range of ISS claimed.

Based on the foregoing, one skilled in the art would have to practice undue experimentation in order to practice the claimed invention. The specification therefore fails to enable the invention of claims 1-6 and 8-15.

Claim Rejections - 35 USC § 102

[1] Marshall, J.D. (2005) DNA and Cell Biol. 24, 2, 63-72.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 1-4, 6 and 8-14 are rejected under 35 U.S.C. 102(e) as being anticipated by Davis et al. (US 6,406,705). Regarding claims 1-4, 6, 8 and 9, Davis teaches a method for suppressing respiratory syncytial virus infection in an individual comprising administering an ISS to the respiratory tract of said individual (col. 8, lines 56-62; col. 15, line 65; col. 16, line 67; col. 17, line 1; and col. 31, lines 49-60), wherein said ISS is greater than 6 and less that 200 nucleotides in length (col. 4, lines 18-19), wherein neither a viral antigen nor an immunostimulatory cytokine is coadministered with said ISS (col. 3, lines 4-6), and wherein said composition is administered in an amount sufficient to suppress an RSV infection (col. 9, lines 29-32). Davis further teaches performing its method by administering an ISS having the sequence 5'-CACGTTCC-3' (col. 30, line 30). Davis also teaches administering the ISS to the nasal passages and the lungs (col. 31, lines 58-60).

Regarding claim 10, the Examiner notes that the limitation "wherein the suppression comprises a reduction of RSV titer in a biological sample from said individual" is inherent to the teachings of Davis for the reasons stated in the previous Office action.

Claim Rejections - 35 USC § 103

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 11-14 are rejected under 35 U.S.C. §103(a) as being unpatentable over Davis. Davis teaches all the limitations discussed under 1-4, 6 and 8-10. Davis does not expressly teach

assembling the ISS sequence into a kit wherein said kit lacks RSV antigen and an immunostimulatory cytokine. However, assembling reagents in preparation for an experiment is well within the knowledge generally available to one skilled in the art. Moreover, assembling reagents ensures that all the components necessary for an experiment are present. Accordingly, it would have been obvious at the time of Applicant's invention to assemble Davis' ISS into a kit in order to facilitate the execution of its method. Note the disclosure of Davis would serve as instructions for administering the ISS sequence.

Response to Arguments

Enablement

Applicant argues the rejection of the claims under 35 U.S.C. 112, first paragraph is improper because the Examiner is requiring human clinical data in order to enable the breadth of the present claims. However, this argument ignores the potential of *in vitro* assays based on human cell models. For example, using the claimed ISS in a whole-cell assay based on human PBMC could be used as a measure of human efficacy. Accordingly, Applicant's argument is not persuasive.

Applicant further argues that the specification does not need to provide working examples for every host that is capable of being treated by the claimed invention. Applicant points out that MPEP section 2164.02 provides that an animal model my function as a working example if the example correlates with claimed invention. Applicant further points out that the cotton rat model correlates with the claimed invention because it is an accepted model for RSV study. The Examiner respectfully submits that Applicant's cotton rat examples do not correlate

with the invention. Here, the invention relates to suppressing RSV infection using an ISS in any animal without the administration of an antigen or other immunomodulating agent. There is no indication in the art or the specification that indicates that the cotton rat model serves as an accepted model for how humans or other mammals respond to ISS. In fact, research indicates humans do not react to ISS in the same way as lab models (see enablement rejection). Accordingly, Applicant's examples fail to enable using the claimed method across the breadth of species claimed.

Applicant argues the Office action's reliance on Silverman is misplaced because Silverman's teachings relate to "generalizations." Applicant notes the invention is not a generalization because the claims are limited to RSV, an ISS of a "specific" length, and the administration of ISS at a specific site (i.e. the respiratory tract). The Examiner respectfully submits these limitations fail negate Silverman. First, the claimed method relates to administering any 5-CG-3' oligonucleotide between 7 and 200 bases. Given the length of the potential length and variation at each base, the claimed ISS is capable of taking on a great number of sequences. Thus, the invention cannot be said to require a specific oligonucleotide as Applicant claims. Also, whether or not Silverman proves a lack of enablement does not turn on the claimed invention being a generalization. Rather, Silverman demonstrates that achieving results across species is complicated by a number of highly variable factors. Accordingly, Silverman shows the use of ISS across species is unpredictable.

Applicant makes a number of arguments in arguing the specification enables the range of ISS called out in the claims. This argument however is moot in view of the new grounds of

rejection discussed under 35 U.S.C. 112, first paragraph above. That is, the present enablement rejection does not concern the size range of ISS claimed.

Written Description

The rejection of claims 1-7 and 8-15 under the written description provisions of 35 U.S.C. 112, first paragraph is withdrawn in view of Applicant's remarks.

Art Rejection of Claims 1-4, 6 and 8-14 Under Davis (US 6,406,705 B1)

Applicant argues Davis does not teach or suggest the claimed invention because Davis only administers ISS in combination with antigen and adjuvants. Regarding the portions of Davis cited, Applicant urge that the following anticipatory language takes the invention out of context: "the Th1 response can be induced using CpG DNA alone, or in combination with a[n] . . . adjuvant . . . ." The Examiner respectfully disagrees.

The portion of Davis Applicant refers to is taken from a paragraph that begins "[a]ccording to another aspect of the invention a method of inducing a Th1 immune response in a subject is provided" (see e.g. col. 2, lines 55-56, emphasis added). This language is preceded by a paragraph which states "[t]he CpG oligonucleotide and the non-nucleic acid adjuvant may be administered with any or all of the administrations of antigen" (col. 2, lines 31-33), which is followed by the paragraph beginning "[t]he antigen may be any type of antigen known in the art" (col. 2, line 44). Thus, by beginning with "[a]ccording to another aspect of the invention . . .," the paragraph relied upon in the rejection obviously refers to a separate embodiment wherein ISS is not administered with adjuvant or antigen. It is also worth noting that relied upon language

(lines 55-56) refers to inducing a Th1 immune response which is precisely what Kobayashi et al. state is the effect of administering ISS without adjuvant.

Applicant argues that the anticipatory language of Davis does not disclose the invention because Davis states "the same method is performed . . . using CpG DNA alone, or CpG DNA in combination with a non-nucleic acid adjuvant . . . at the same or different time." Applicant reasons that the language stating "CpG DNA alone" refers to the use of CpG DNA as the only adjuvant and not the use of CpG DNA without antigen as called for in the claims. The Examiner respectfully disagrees. The language "the same method" (col. 3, line 3) is obviously referring to the method of inducing a Th1 response which was introduced at the beginning of the paragraph where "the same method" was first introduced. This is clear in that the beginning of the paragraph provides "a method of inducing a Th1 immune response . . ." (col. 2, lines 55-56), while the relied-upon language (from the same paragraph) states "the Th1 response can be induced using CpG DNA alone . . . " (col. 3, line 4). Accordingly, the relied-upon portion of Davis anticipates the claimed subject matter.

Applicant argues the rejection of the claims as obvious over Davis is improper because there is no motivation to modify Davis to arrange its reagents into a kit. The Examiner respectfully submits that one skilled in the art would readily recognize the convenience of collecting the reagents required for an assay. Accordingly, it would have been obvious to the skilled artisan to arrange the claimed composition into kit.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Timothy M. Brown whose telephone number is (571) 272-0773. The examiner can normally be reached on Monday - Friday, 8am - 5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Housel can be reached on (571) 272-0902. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Timothy M. Brown
Examiner
Art Unit 1648

tmb

JAMES HOUSEL
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600

10/17/05

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